UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	MDL Docket No. 2738
This Document Relates To All Cases	

DEFENDANTS JOHNSON & JOHNSON AND LLT MANAGEMENT, LLC'S MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE PLAINTIFFS' EXPERTS' OPINIONS REGARDING BIOLOGICAL PLAUSIBILITY/MECHANISM

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Plaintiffs' experts generally hypothesize a multi-step chain by which talc applied to the external perinium could cause the diverse group of diseases that are collectively referred to as ovarian cancer. According to these experts: (1) talc migrates into the vagina and up the reproductive tract all the way to the ovaries or fallopian tubes, or, alternatively, is inhaled and distributed throughout the body; (2) once it reaches the tubes and ovaries, it causes inflammation and oxidative stress and/or impairs immune surveillance of early cancer cells; and (3) some combination of these events leads to ovarian cancer. To be admissible under Federal Rule of Evidence 702, every step in this chain must be supported by reliable evidence. None of them are. Although Judge Wolfson largely denied a similar motion,[1] her ruling, which held that the lack of sufficient support for plaintiffs' experts' theories presented a question of weight rather than admissibility, represents exactly the kind of error that the recent revisions to Rule 702 were intended to correct. Plaintiffs' experts' biological plausibility opinions should therefore be excluded.[2]

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[1] Judge Wolfson's ruling only addressed the experts that testified live at the *Daubert* hearing, including Drs. Arch Carson, Anne McTiernan, and Daniel Clarke-Pearson. She indicated that her "reasoning" would apply to "the remainder of the pending *Daubert* motions." *In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Pracs. & Prods. Litig.*, 509 F. Supp. 3d 116, 128-29 & n.3 (D.N.J. 2020).

[2] The following plaintiffs' experts seek to testify on biological plausibility: Arch Carson, Daniel Clarke-Pearson, Michele Cote, Bernard Harlow, Sarah Kane, *(cont'd)*

First, plaintiffs' experts all fail to address the biological plausibility question in a reliable manner because they conflate different subtypes of ovarian cancer, which constitute different diseases that develop in different tissues with different risk factors and causes. Judge Wolfson gave short shrift to this issue, but without specifying which subtype(s) of ovarian cancer are supposedly caused by perineal talc use, plaintiffs' experts cannot even begin to formulate a scientifically coherent theory of the mechanism by which that might happen.

Second, plaintiffs' experts lack reliable scientific evidence that talc applied externally can travel all the way to the fallopian tubes or ovaries. As even Judge Wolfson acknowledged, no human study has ever shown that any particle can migrate from the external perineum to the ovaries; rather, the experts rely on studies of substances inserted deep into the internal genital tract, often with women kept in an unnatural position such as with the legs up. This presents an insurmountable analytical gap that cannot be plugged by made-for-litigation reports that purport to find talc in pathology samples of reproductive tissue, since there is no way to know the origin of the talc or talc-like substances.

Shawn Levy, Anne McTiernan, Patricia Moorman, Laura Plunkett, Jack Siemiatycki, Sonal Singh, Ellen Blair Smith, Rebecca Smith-Bindman and Judith Wolf. Plaintiffs' expert Dr. Ghassan Saed, whose opinions were rejected in large part by Judge Wolfson, was recently withdrawn by plaintiffs' counsel, but his work continues to form the basis of the remaining experts' biological mechanism opinions.

A few plaintiffs' experts halfheartedly advance an alternative theory that talc can be inhaled and then distributed throughout the body through the lymphatic system, including to the ovaries and tubes. This hypothesis, which Judge Wolfson correctly excluded last time, has even less support.

Third, even if it were plausible that cosmetic talc could migrate to the ovaries or fallopian tubes, there is no reliable evidence that it would cause chronic inflammation or oxidative stress when it got there. Since no one has ever found histologic evidence of inflammation in the ovaries of human talc users, the experts rely on a series of in vitro or animal studies that show either non-neoplastic changes in animal tissue, or more commonly, scattered subcellular changes in a petri dish or test tube. They rely most heavily on a series of studies that plaintiffs' counsel solicited from former expert Dr. Ghassan Saed, but those studies have been heavily criticized by Dr. Saed's peers as containing "problems . . . too numerous to count."[3] Even taken at face value, they fall well short of reliably showing inflammation or oxidative stress, much less of causing carcinogenic transformation—a claim that one reviewer called "outrageous."[4]

Fourth, plaintiffs' experts lack reliable evidence that chronic inflammation

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[3] (SAED_SEPT222021_SUPPL_000104 ("SAED" documents attached collectively as Ex. 1 to the Decl. of Jessica Davidson ("Davidson Decl.")).)

[4] (SAED_SEPT222021_SUPPL_000101.)

or oxidative stress (supposedly caused by talcum powder) can cause ovarian cancer. The experts primarily contend that these conditions can lead to malignant transformation—i.e., the transformation of a normal healthy cell to a cancer cell. Once again, however, these opinions lack any support in the literature, and plaintiffs' experts resort to vastly overstating what the studies on which they rely actually say.

Fifth, and finally, a few plaintiffs' experts suggest that talc-indued inflammation or oxidative stress reduces immune system functions that would ordinarily destroy early cancer cells before they form a tumor. This hypothesis is based on even thinner evidence: two *in vitro* studies that are too far afield and limited to support the experts' theories.

ARGUMENT

As set forth in defendants' motion to exclude plaintiffs' experts' general causation opinions (incorporated herein), Rule 702 requires the proponent of expert testimony to demonstrate by a preponderance of the evidence that the experts' opinions are "the product of reliable principles and methods" that have been "reliabl[y] appli[ed] . . . to the facts of the case." Fed. R. Evid. 702(c)-(d). "[T]he sufficiency of the basis of an expert's" opinion is a question for the judge, to "be decided under Rule 702." *Id.*, advisory committee's notes to 2000 amendment.

With respect to biological plausibility in particular, Judge Wolfson found it

sufficient to show merely that a proposed mechanism "is credible in light of what is known from science and medicine about the human body and the potentially offending agent." *In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Pracs. & Prods. Litig.*, 509 F. Supp. 3d 116, 174 (D.N.J. 2020) (citation omitted). She also appeared to reverse the burden of proof, suggesting that a speculative theory would suffice until defendants could prove it wrong. *Id.* at 175 (a theory is plausible as long as it has not "been disproven as a matter of science").

Rule 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), require more than the mere speculation that Judge Wolfson found sufficient. Specifically, a biological plausibility expert must "explain to the requisite reasonable degree of medical certainty the biological and/or pathological mechanism by which" the substance at issue causes the harm alleged. *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 534, 561-62 (W.D. Pa. 2003) ("While *Daubert* does not require absolute precision in identifying the medical mechanism of injury, there still must be 'sufficiently compelling proof that the agent must have caused the damage somehow.'") (citations omitted); *see, e.g.*, *Wade-Greaux v. Whitehall Lab'ys, Inc.*, 874 F. Supp. 1441, 1464 (D.V.I. 1994) (excluding biological mechanism opinions that were "speculative and not subject to proof"), *aff'd*, No. 94-7199, 1994 WL 16973481 (3d Cir. Dec. 15, 1994). A "biological explanation without evidence of the mechanism by which it works is merely an

unproven hypothesis, a theory." *In re Accutane Prods. Liab. Litig.*, 511 F. Supp. 2d 1288, 1295 (M.D. Fla. 2007); *In re Acetaminophen – ASD-ADHD Prods. Liab. Litig.*, MDL No. 3043, 2023 WL 8711617, at *30 (S.D.N.Y. Dec. 18, 2023).

Moreover, where, as here, experts propose a multi-step theory, they must support every necessary link with "evidence" sufficient "to carry them all the way down their causal chain." *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 426 (S.D.N.Y. 2005); *see, e.g.*, *In re Incretin-Based Therapies Prods. Liab. Litig.*, 524 F. Supp. 3d 1007, 1041-42 (S.D. Cal. 2021) ("must support 'every necessary link' in [his or her] biological theory with supporting evidence"). That is consistent with the general principle that "good grounds must support each step of the [expert's] analysis and '*any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible.'" *In re Human Tissue Prods. Liab. Litig.*, 582 F. Supp. 2d 644, 656 (D.N.J. 2008) (quoting *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 745 (3d Cir. 1994)); *see also Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) ("A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.").

Finally, as even the cases Judge Wolfson cited acknowledge, "the significance of th[e biological plausibility] factor increases," where, as here, "epidemiological evidence is . . . inconclusive." *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 181 (S.D.N.Y. 2009) (cited in *In re Johnson & Johnson*, 509

F. Supp. 3d at 174).

The recent decision in *In re Acetaminophen* is instructive. In that case, the plaintiffs' experts sought to opine on mechanisms by which exposure to acetaminophen in utero could plausibly cause neurodevelopmental disorders. The court excluded those opinions because "the precise physiological process or processes by which the[relevant] conditions . . . develop are unknown" and "scientists had at best developed hypotheses." *In re Acetaminophen*, 2023 WL 8711617, at *30. Specifically, the *Acetaminophen* court highlighted the lack of "replicated data showing that prenatal exposure to clinically relevant doses of acetaminophen causes" the changes alleged to occur "in the fetal brain." *Id.* at *38. And it noted that the results of animal studies were "highly variable." *Id.* at *39. All told, the experts could "not reliably fill two critical gaps in" their mechanistic theory, and therefore their biological plausibility opinions had to be excluded. *Id.* at *40.

The authorities Judge Wolfson cited do not support the watered-down standard she applied. Her order first quotes the Reference Manual on Scientific Evidence for the proposition that "an observation . . . inconsistent with current biological knowledge . . . should not be disregarded." *In re Johnson & Johnson*, 509 F. Supp. 3d at 172 (citation omitted). But the question is not whether epidemiologic evidence should be "disregarded" altogether; rather, the question is

whether the biological plausibility prong of Bradford Hill supports a causal interpretation, particularly in light of weak and inconsistent epidemiology.

The cases that Judge Wolfson relied on are no more supportive. The first, *Milward v. Acuity Specialty Products Group, Inc.*, 639 F.3d 11 (1st Cir. 2011) (cited in *In re Johnson & Johnson*, 509 F. Supp. 3d at 174-75), was described by the chair of the subcommittee that drafted the recent amendments to Rule 702 as a "prime example of the problem" that the amendments were intended to solve, Thomas D. Schroeder, *Toward a More Transparent Approach to Considering the Admission of Expert Testimony*, 95 Notre Dame L. Rev. 2039, 2043-44 (2020). Judge Wolfson also repeatedly cited *In re Abilify (Aripiprazole) Products Liability Litigation* for the proposition that "biological plausibility does not require proof of the mechanism." *In re Johnson & Johnson*, 509 F. Supp. 3d at 174-75 (citing 299 F. Supp. 3d 1291, 1308, 1335-36 (N.D. Fla. 2018)). But *Abilify* merely states that an expert's opinion need not be "biologically certain" because "arguably, there are no certainties in science." *In re Abilify*, 299 F. Supp. 3d at 1335-36 (quoting *Daubert*, 509 U.S. at 590) (cited in *In re Johnson & Johnson*, 509 F. Supp. 3d at 175). That does not mean that any hypothesis suffices. *Abilify* itself, for example, involved a proposed multi-step mechanism that had been "demonstrated via peer-reviewed, published *in vivo* studies," *id.* at 1336, that was "consistent with the FDA's assessment," *id.* at 1344. And *In re Fosamax*, another case on which Judge

Wolfson relied, involved a mechanism that had been shown directly in rats and dogs, and was so widely accepted that "[n]early every report and review of [the condition] point[ed] to" the proposed mechanism "as a likely" one. 645 F. Supp. 2d at 182 (citation omitted) (cited in *In re Johnson & Johnson*, 509 F. Supp. 3d at 174). Even in that context, the court prohibited any mechanistic testimony unless it was "qualified . . . by a statement that it remains a theory that . . . might be . . . disproved." *Id.* at 183.

Under the proper standard, plaintiffs' experts' mechanistic hypotheses are unreliable, and their biological plausibility opinions should therefore be excluded.

I. PLAINTIFFS' EXPERTS' BIOLOGICAL PLAUSIBILITY THEORIES PROCEED FROM THE ERRONEOUS PREMISE THAT OVARIAN CANCER IS A UNITARY DISEASE.

Plaintiffs' experts conflate a host of different diseases under the umbrella term "ovarian cancer," even though those diseases have different causes and risk factors. Judge Wolfson barely addressed this flaw, despite acknowledging that "epithelial ovarian cancer may have various subtypes." *In re Johnson & Johnson*, 509 F. Supp. 3d at 181, 182-83.

Conflating different diseases, with different etiologies, is unscientific even if those diseases are closely related, and an expert opinion that does so is inherently unreliable. *See, e.g.*, *Hoefling v. U.S. Smokeless Tobacco Co.*, 576 F. Supp. 3d 262, 272-73 (E.D. Pa. 2021) (excluding expert who sought to opine that smokeless

tobacco could cause tonsil cancer based on studies that "found a causative link only to oral-cavity, esophageal and pancreatic cancer" because various forms of "'head and neck cancer' . . . have different risks"); *Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1371 (N.D. Ga. 2001) (excluding opinion that medication could cause hemorrhagic stroke, when evidence only linked it to ischemic stroke because "ischemic strokes and hemorrhagic strokes are distinct and have different *modi operandi*").

Much like "head and neck cancer" or "stroke," "epithelial ovarian cancer" is an umbrella term for several diseases that arise in different tissues, each with its own risk factors.[5] Plaintiffs' experts acknowledge as much.[6] These distinctions

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[5] *See* CDC, Ovarian Cancer Basics, https://www.cdc.gov/ovarian-cancer/about/index.html (last visited July 11, 2024) ("ovarian cancer is ***a group*** of diseases that originates in the ovaries," fallopian tubes, or peritoneum); Wentzensen & O'Brien, *Talc, Body Powder, and Ovarian Cancer: A Summary of the Epidemiologic Evidence*, 163(1) Gynecol. Oncol. 199, 202 (2021) (Ex. 2 to Davidson Decl.) ("Ovarian cancer is characterized by profound heterogeneity that can be observed in site of origin, genetic susceptibility, somatic mutations, molecular pathways, risk factor associations and morphological differences.").

[6] (*See, e.g.*, 3d Am. Rep. of Rebecca Smith-Bindman ("Smith-Bindman 3d Am. Rep.") at 7, May 28, 2024 (Ex. 3 to Davidson Decl.) ("Ovarian cancers (epithelial and non-epithelial) are a ***heterogeneous group*** of malignancies that vary in their pathological appearance, molecular biology, risk factors, etiology, and prognosis.") (emphasis added); 3d Am. Rep. of Judith Wolf ("Wolf 3d Am. Rep.") at 3, May 28, 2024 (Ex. 4 to Davidson Decl.) (similar); Dep. of Patricia G. Moorman 225:4-9, Feb. 13, 2024 (Ex. 5 to Davidson Decl.) (agreeing that "[t]he data suggest[] that there are several etiologically distinct types of cancers that manifest in the ovaries").)

mean that the various diseases referred to as ovarian cancer arise in different places: serous cancer, primarily (but not always) in the fimbria (fringe tissue) of the fallopian tubes near the ovaries in contrast to endometrioid cancers, and likely clear cell cancers, which typically arise from uterine endometrial tissue that is growing abnormally outside the uterus.[7]

These cancers also arise in different ways and are associated with different risk factors, as plaintiffs' experts concede.[8] For instance, endometriosis (a condition involving abnormal growth of tissue outside the uterus) is a huge risk factor for clear cell and endometrioid ovarian cancer, but not high-grade serous cancers.[9] Among environmental or lifestyle factors, smoking is associated with an increase in mucinous cancer but not associated (at least not positively) with any other ovarian cancers.[10] Obesity is associated with an increased risk for several forms of ovarian cancer, but not an increased risk of high grade serous, the most

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[7] *See* Karnezis, *The Disparate Origins of Ovarian Cancers: Pathogenesis & Prevention Strategies*, 17(1) Nat. Rev. Cancer 65 (2017) (Ex. 6 to Davidson Decl.).

[8] (*See, e.g.*, Smith-Bindman 3d Am. Rep. at 9 ("Risk factors vary by cancer type" and giving as an example the association between smoking and mucinous cancer).)

[9] *See* Reid, *Epidemiology of Ovarian Cancer: A Review*, 14(1) Cancer Biol. Med. 9 (2017) ("Reid 2017") (Ex. 7 to Davidson Decl.).

[10] *See* Collaborative Group on Epidemiological Studies of Ovarian Cancer, *Ovarian Cancer and Smoking: Individual Participant Meta-Analysis Including 28,114 Women With Ovarian Cancer From 51 Epidemiological Studies*, 13(9) Lancet Oncology 946 (2012) (Ex. 8 to Davidson Decl.).

frequent and most deadly. Talc is no different: Dr. Smith-Bindman specifically contends that "the importance of talcum powder products as a risk factor . . . [may] vary by type."[11]

Nonetheless, plaintiffs' experts do not consider whether their proposed mechanisms would plausibly cause the different gene mutations at different tissue sites necessary to account for different subtypes. Indeed, ***not a single plaintiffs' expert*** even mentions the distinctions between subtypes as a part of the discussion of biological mechanism in their reports.[12] Some experts, like Dr. Smith-Bindman, barely seem to understand the distinctions.[13] Others bolster their conclusions by pointing to conditions, such as endometriosis, which are only associated with particular types of ovarian cancer.[14]

Plaintiffs' experts' failure to address how their mechanism theories relate to

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[11] (Smith-Bindman 3d Am. Rep. at 7; Dep. of Rebecca Smith-Bindman ("10/1/21 Smith-Bindman Dep.") 54:24-25, Oct. 1, 2021 (Ex. 9 to Davidson Decl.) ("less precision" for association between talc and non-serous cancers).)

[12] (*See, e.g.*, Dep. of Sonal Singh ("4/4/24 Singh Dep.") 35:12-36:10, Apr. 4, 2024 (Ex. 10 to Davidson Decl.) (confirming testimony "not broken down by histological subtype").)

[13] (*See* 10/1/21 Smith-Bindman Dep. 182:20-183:10 (does not know whether various cancers are classified as Type I or Type II).)

[14] (2d Am. Rep. of Shawn Levy ("Levy 2d Am. Rep.") at 14, May 28, 2024 (Ex. 11 to Davidson Decl.); Rep. of Sarah E. Kane ("Kane Rep.") at 10, Nov. 15, 2018 (Ex. 12 to Davidson Decl.); 3d Am. Rep. of Anne McTiernan ("McTiernan 3d Am. Rep.") at 91, May 28, 2024 (Ex. 13 to Davidson Decl.).)

the different ovarian cancer subtypes is even more problematic now than it was when defendants raised it previously. The recent selection of bellwether plaintiffs highlights the issue. Among those plaintiffs, two had high grade serous ovarian cancer (Ms. Judkins and Ms. Rausa);[15] two had endometrioid cancer (Ms. Gallardo and Ms. Newsome);[16] and two had clear cell cancer (Ms. Bondurant and Ms. Converse).[17] Only by treating these three diseases as one and the same can plaintiffs' experts offer an opinion applicable to all of them.

In addition, the experts now emphasize a series of recent in vitro studies that purported to show transformation in ovarian epithelial cells.[18] That result has

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[15] (*See* 2d Am. Rep. of Judith Wolf at 23, *Judkins v. Johnson & Johnson*, May 28, 2024 (Ex. 14 to Davidson Decl.); 2d Am. Rep. of Daniel L. Clarke-Pearson at 16, *Rausa v. Johnson & Johnson*, May 28, 2024 (Ex. 15 to Davidson Decl.).)

[16] (*See* 2d Am. Rep. of Judith Wolf at 22, *Gallardo v. Johnson & Johnson*, May 28, 2024 (Ex. 16 to Davidson Decl.); 2d Am. Rep. of Daniel L. Clarke-Pearson at 16, *Newsome v. Johnson & Johnson*, May 28, 2024 (Ex. 17 to Davidson Decl.).)

[17] (*See* 2d Am. Rep. of Judith Wolf at 23, *Bondurant v. Johnson & Johnson*, May 28, 2024 (Ex. 18 to Davidson Decl.); 2d Am. Rep. of Daniel L. Clarke-Pearson at 16, *Converse v. Johnson & Johnson*, May 28, 2024 (Ex. 19 to Davidson Decl.).)

[18] Harper, *Talcum Powder Induces Malignant Transformation in Normal Human Primary Ovarian Epithelial Cells*, 75(2) Minerva Obstet. Gynecol. 150 (2023) ("Harper 2023") (Ex. 20 to Davidson Decl.) (cited in 3d Am. Rep. of Daniel L. Clarke-Pearson ("Clarke-Pearson 3d Am. Rep.") at 5-6, May 28, 2024 (Ex. 21 to Davidson Decl.); Suppl. Rep. of Sonal Singh ("Singh Suppl. Rep.") at 13, Nov. 15, 2023 (Ex. 22 to Davidson Decl.); Smith-Bindman 3d Am. Rep. at 14; Wolf 3d Am. Rep. at 16).) Dr. Saed was the primary and corresponding author even though Dr. Harper's name is listed first.

minimal relevance to serous ovarian cancer, which arises in the fimbriae of the fallopian tubes, and none at all to endometrioid or clear cell cancer (the diseases that afflict four of the six bellwether plaintiffs) since, as discussed, those do not arise anywhere nearby. The same is true of a 2020 study by Mandarino and colleagues,[19] which looked at the interaction between macrophages and ovarian epithelial cells from mice.

In sum, plaintiffs' experts' mechanism opinions are not tied to what is known about how and where various subtypes of ovarian cancers arise. This alone renders them unreliable and requires exclusion of plaintiffs' experts' biological plausibility opinions.

II. THERE IS NO RELIABLE EVIDENCE THAT PERINEALLY-APPLIED TALC CAN REACH THE FALLOPIAN TUBES OR OVARIES.

Plaintiffs' primary migration theory is that talc applied to the external perineum enters the vagina and migrates against the flow of gravity and vaginal and cervical mucus upwards to the fallopian tubes and ovaries. Judge Wolfson found plaintiffs' retrograde migration theory admissible, even though she conceded

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[19] Mandarino, *The Effect of Talc Particles on Phagocytes in Co-Culture With Ovarian Cancer Cells*, 180 Environ. Res. 108676 (2020) ("Mandarino 2020") (Ex. 23 to Davidson Decl.) (cited in Clarke-Pearson 3d Am. Rep. at 6, 13, 14; Am. Rep. of Michele L. Cote ("Cote Am. Rep.") at 14, 38, May 28, 2024 (Ex. 24 to Davidson Decl.); Levy 2d Am. Rep. at 16; McTiernan 3d Am. Rep. at 91; 3d Am. Rep. of Laura M. Plunkett ("Plunkett 3d Am. Rep.") at 28, 46, May 28, 2024 (Ex. 25 to Davidson Decl.); Singh Suppl. Rep. at 13, 15, 23; Wolf 3d Am. Rep. at 16).

that migration has never been demonstrated in circumstances analogous to perineal dusting. *In re Johnson & Johnson*, 509 F. Supp. 3d at 174. Under Rule 702, that should have required exclusion of the experts' opinions. A few plaintiffs' experts also continue to advance an alternative theory that talc can reach the ovaries through inhalation. Judge Wolfson correctly excluded this theory and it remains devoid of support.

A. The Experimental Studies Involving Humans Do Not Support Plaintiffs' Experts' Opinions.

Plaintiffs cite a series of studies that show particles migrating after they were inserted deep within a human or animal vagina and the subject was placed in a position to maximize migration.[20] They also cite a couple of studies related to a phenomenon known as retrograde menstruation. These studies cannot support an opinion that non-motile talc particles can travel from the external perineum to the ovaries for several reasons.

First, none of the human studies involved "***externally applied*** talc." *In re*

[20] Egli & Newton, *The Transport of Carbon Particles in the Human Reproductive Tract*, 12(2) Fertil. Steril. 151 (1961) ("Egli & Newton 1961") (Ex. 26 to Davidson Decl.) (cited in *In re Johnson & Johnson*, 509 F. Supp. 3d at 173). Egli and Newton 1961, like many of the studies at issue, sought to study fertilization, which explains why particles were deposited deep into the vagina (like sperm would be) as well as other study design choices that promoted migration.

Johnson & Johnson, 509 F. Supp. 3d at 174 (bold added).[21] Instead, the particle-transport studies involved material inserted deep into the internal reproductive tract, and therefore much closer to the target tissue. For instance, in three articles cited in a long block quotation in Judge Wolfson's order, the particles were placed at the posterior end of the vagina or cervical opening.[22] Likewise, to the extent the experts rely on reports of retrograde menstruation,[23] that involves blood flow from the uterus to the tubes, not from the vagina, much less the external environment.

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[21] (*See also* Dep. of Michele L. Cote ("3/21/24 Cote Dep.") 180:17-24, Mar. 21, 2024 (Ex. 27 to Davidson Decl.) (acknowledging that there are no studies of perineal talc exposure).)

[22] *See* Egli & Newton 1961 at 152-53 ("deposited in the posterior fornix") (cited, *e.g.*, in Rep. of Arch Carson ("Carson Rep.") at 7, Nov. 16, 2018 (Ex. 28 to Davidson Decl.); Clarke-Pearson 3d Am. Rep. at 12; Cote Am. Rep. at 13; McTiernan 3d Am. Rep. at 88; Plunkett 3d Am. Rep. at 31, 32; Wolf 3d Am. Rep. at 14); Venter & Iturralde, *Migration of a Particulate Radioactive Tracer From the Vagina to the Peritoneal Cavity and Ovaries*, 55(23) S. Afr. Med. J. 917, 917-18 (1979) ("Venter & Iturralde 1979") (Ex. 29 to Davidson Decl.) ("deposited in the posterior fornix") (cited in *In re Johnson & Johnson*, 509 F. Supp. 3d at 173 & *e.g.*, in Carson Rep. at 7; Clarke-Pearson 3d Am. Rep. at 12; McTiernan 3d Am. Rep. at 88, 89; Wolf 3d Am. Rep. at 14); Kunz, *The Uterine Peristaltic Pump: Normal and Impeded Sperm Transport Within the Female Genital Tract*, *in* The Fate of the Male Germ Cell 267, 270 (Ivell & Holstein eds. 1997) (Ex. 30 to Davidson Decl.) ("at the external os of the uterine cervix") (cited in *In re Johnson & Johnson*, 509 F. Supp. 3d at 173 & Plunkett 3d Am. Rep. at 31, 38-39, 41; Wolf 3d Am. Rep. at 14).

[23] *See* Blumenkrantz, *Retrograde Menstruation in Women Undergoing Chronic Peritoneal Dialysis*, 57(5) Obstet. Gynecol. 667 (1981) (Ex. 31 to Davidson Decl.) (cited in Plunkett 3d Am. Rep. at 31; Wolf 3d Am. Rep. at 14); Halme, *Retrograde Menstruation in Healthy Women and in Patients With Endometriosis*, 64(2) Obstet. Gynecol. 151 (1984) (Ex. 32 to Davidson Decl.) (cited in Carson Rep. at 7; Wolf 3d Am. Rep. at 14).

Obviously the longer the distance the particles need to travel, the less likely they are to make it there. One study cited by plaintiffs' experts shows as much: it inserted India ink into either the vagina, cervical canal or uterus and showed transit to the fallopian tubes in a majority of uterine injections, but almost never in cases of vaginal deposition.[24] Moreover, external dusting is categorically different from any kind of internal application since the particles would need to migrate (against gravity)[25] past the labia majora and minora to even enter the reproductive tract in the first place. Beyond scattered references to the female genitalia as an "open system," plaintiffs' experts do not consider this fact. The fundamental disjunction between the studies on which the experts rely and the conclusion they draw from them does not represent a lack of metaphysical certainty; it represents an insurmountable "analytical gap," *Joiner*, 522 U.S. at 146, that warrants exclusion.

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[24] de Boer, *Transport of Particulate Matter Through the Human Female Genital Tract*, 28(2) J. Reprod. Infertil. 295 (1972) ("de Boer 1972") (Ex. 33 to Davidson Decl.) (cited in Cote Am. Rep. at 13; Plunkett 3d Am. Rep. at 32). In one striking example of the extent to which plaintiffs' experts cherry-pick data, Dr. Cote notes that "at least half" of the particles deposited in the uterus reached the fallopian tubes while ignoring the obviously more-relevant results from the vagina.

[25] Dr. Plunkett argues that gravity is not a concern because the vagina has "two distinct portions" and the "upper portion . . . lies . . . almost horizontal" and at a 130-degree angle from the lower portion. (Plunkett 3d Am. Rep. at 31 (citation omitted).) That actually shows that the effect of gravity would be reduced ***once a particle reaches the upper vagina***. In other words, it demonstrates the difference between studies that insert particles in the posterior portion of the vagina and external dusting.

Second, the experts' reliance on particle-transport studies raises two additional analytical gaps that Judge Wolfson did not even mention, both of which mean there is no reliable basis to extrapolate from those study results to perineal dusting. For starters, none of the human studies involved talc; rather, they involved substances such as carbon or albumin microspheres,[26] and they do not purport to predict how talc particles, with different sizes or properties, might move. As Dr. Cote testified, those studies do not "mimic" talc and were not intended to.[27] In addition, in every study plaintiffs' experts cited, researchers took steps to increase the likelihood that the inserted particles would reach the upper reproductive tract. All involved women lying down, sometimes with intentionally elevated pelvises such that gravity would promote migration, and often held in position for hours.[28] Some study authors took further steps to force the inserted

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[26] *See, e.g.*, Egli & Newton 1961 (carbon particles); Venter & Iturralde 1979 (radiolabeled albumen microspheres); Sjösten, *Retrograde Migration of Glove Powder in the Human Female Genital Tract*, 19(4) Hum. Reprod. 991 (2004) ("Sjösten 2004") (Ex. 34 to Davidson Decl.) (cited in Carson Rep. at 7; Cote Am. Rep. at 14; Clarke-Pearson 3d Am. Rep. at 12; Plunkett 3d Am. Rep. at 31, 39; Wolf 3d Am. Rep. at 14) (glove powder, likely cornstarch). The retrograde menstruation studies obviously involved blood, not talc.

[27] (3/21/24 Cote Dep. 181:10-17.)

[28] *See, e.g.*, Egli & Newton 1961 at 152 ("lithotomy position with . . . head tilted downward" and remained in position for duration of a hysterectomy, which takes hours); Venter & Iturralde 1979 at 917-18 ("supine [gynecologic examination] position with the buttocks slightly elevated" and "kept in this position for" two hours). One study frequently cited by plaintiffs' experts did not *(cont'd)*

particles to stay in the internal genital tract.[29] Others administered oxytocin, a medication to induce muscle contractions.[30] If there is a way to reliably extrapolate from these studies to ordinary perineal talc dusting, plaintiffs' experts do not offer it; instead, they ignore the artificial conditions altogether.

B. Animal Studies Do Not Offer Reliable Proof Of Migration.

Some plaintiffs' experts use animal studies to prop up their migration theory, even though others acknowledge they are unsupportive.[31] These studies offer even less support that the human studies discussed above. Only one such study involved externally applied talc, but the talc was applied in enormous quantities not analogous to human exposure.[32] More importantly, animal studies are not admissible to prove human causation absent "good grounds to extrapolate from

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expressly report the women's position but involved gynecological examinations, which typically take place with the patient on her back with knees bent and legs slightly elevated. *See* Sjösten 2004.

[29] *See, e.g.*, Venter & Iturralde 1979 at 918 ("vulva was covered with a sanitary towel, and the legs were pressed together to prevent the [solution] streaming from the vagina and thus lowering count levels").

[30] *See* Egli & Newton 1961; de Boer 1972. Oxytocin is released during sexual intercourse and, as mentioned, many of the studies sought to model fertilization.

[31] (*See, e.g.*, Plunkett 3d Am. Rep. at 37 (animal studies "inconsistent with the human data"); 3/21/24 Cote Dep. 187:6-8 (animal studies are "neutral").)

[32] Keskın, *Does Long-Term Talc Exposure Have a Carcinogenic Effect on the Female Genital System of Rats? An Experimental Pilot Study*, 280 Arch. Gynecol. Obstet. 925 (2009) ("Keskın 2009") (Ex. 35 to Davidson Decl.) (cited in McTiernan 3d Am. Rep. at 90; Wolf 3d Am. Rep. at 16).

animals to humans." *In re Human Tissue*, 582 F. Supp. 2d at 657 (quoting *In re Paoli*, 35 F.3d at 743); *see, e.g.*, *Soldo*, 244 F. Supp. 2d at 547-48 (excluding testimony because "plaintiff's experts did not demonstrate that . . . the species in which these studies were performed[] were sufficiently similar to . . . human being[s]"). Presumably for this reason, some plaintiffs' experts admit that there are not any "good animal models."[33] For example, some of the studies involved rodents, whose genital tracts are dissimilar from human genital tracts in addition to the obvious differences in size (and, thus, distance from the point of application to the ovaries).[34]

Moreover, most of the experts ignore the studies showing no talc migration in monkeys,[35] whose anatomy is far more similar to humans, *see In re Rezulin*, 369 F. Supp. 2d at 425 ("Rats are much further than monkeys from humans . . . ."). In those studies (one a pilot study, and the other a "more definitive" follow-up), the researchers inserted either talc or bone black at the posterior fornix of the vagina of

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33 (4/4/24 Singh Dep. 92:17-93:21.)

34 *E.g.*, Henderson, *The Demonstration of the Migration of Talc From the Vagina and Posterior Uterus to the Ovary in the Rat*, 40(2) Environ. Res. 247 (1986) (Ex. 36 to Davidson Decl.) (cited in McTiernan 3d Am. Rep. at 93; Plunkett 3d Am. Rep. at 31, 35-36).

35 Wehner, *On Talc Translocation From the Vagina to the Oviducts and Beyond*, 24(4) Food Chem. Toxicol. 329 (1986) (Ex. 37 to Davidson Decl.) ("Wehner 1986").

monkeys restrained with their pelvises elevated and cervixes "exposed."[36] The animals were kept restrained after application and dosed with oxytocin. Despite these obviously unnatural conditions, they "failed to find any evidence . . . for translocation."[37] The experts' "fail[ure] to account adequately for contrary evidence" renders their methodology "not reliable." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 461 (E.D. Pa. 2014). The few plaintiffs' experts who do mention the monkey study have no reliable basis for dismissing it. Drs. Plunkett and Singh both mention that the study was funded by an industry trade group,[38] but that is not a methodological critique, and the same experts rely on several studies, like those by Dr. Saed, that were funded by plaintiffs' counsel and/or written by plaintiffs' litigation experts. In fact, Dr. Singh specifically testified that funding sources do not discredit the findings of a paper.[39]

C. Evidence Of Talc Particles In Human Reproductive Tissue Does Not Support Plaintiffs' Experts' Migration Theories.

Plaintiffs' experts also rely on a handful of studies in which researchers purported to identify talc particles in tissue taken from the reproductive tracts of

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36 *See id.*; Wehner, *Do Particles Translocate From the Vagina to the Oviducts and Beyond*, 23(3) Food Chem. Toxicol. 367 (1985) (Ex. 38 to Davidson Decl.).

37 Wehner 1986.

38 (*See* Plunkett 3d Am. Rep. at 36-37; Rep. of Sonal Singh ("Singh Rep.") at 18, 57, Nov. 16, 2018 (Ex. 39 to Davidson Decl.).)

39 (*See* Dep. of Sonal Singh ("1/16/19 Singh Dep.") 358:1-4, Jan. 16, 2019 (Ex. 40 to Davidson Decl.).)

human patients, including two studies cited during the first round of expert reports and motion practice—Henderson 1971[40] and Heller 1996[41]—as well as three more recent 2019 studies co-authored by plaintiffs' experts.[42] These studies do not plausibly show migration either.

Henderson 1971 did not even report whether the women from whom the tissue samples were taken had used talc in their perineal area, much less systematically compare those who did with those who did not, as would have been

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[40] Henderson, *Talc and Carcinoma of the Ovary and Cervix*, 78(3) J. Obstet. Gyn. Br. Comm. 266 (1971) ("Henderson 1971") (Ex. 41 to Davidson Decl.) (cited in Clarke-Pearson 3d Am. Rep. at 7; Cote Am. Rep. at 13; Kane Rep. at 14, 16; McTiernan 3d Am. Rep. at 88, 89; Singh Rep. at 18, 57; Rep. of Ellen Blair Smith ("Smith Rep.") at 16, Nov. 16, 2018 (Ex. 42 to Davidson Decl.).)

[41] Heller, *The Relationship Between Perineal Cosmetic Talc Usage and Ovarian Talc Particle Burden*, 174(5) Am. J. Obstet. Gynecol. 1507 (1996) ("Heller 1996") (Ex. 43 to Davidson Decl.) (cited in Clarke-Pearson 3d Am. Rep. at 12; Cote Am. Rep. at 13; Kane Rep. at 14; McTiernan 3d Am. Rep. at 88, 89; Plunkett 3d Am. Rep. at 31, 37-38; Singh Rep. at 18, 57; Wolf 3d Am. Rep. at 14).

[42] McDonald, *Correlative Polarizing Light and Scanning Electron Microscopy for the Assessment of Talc in Pelvic Region Lymph Nodes*, 43(1) Ultrastruct. Pathol. 13 (2019) ("McDonald 2019a") (Ex. 44 to Davidson Decl.) (cited in Plunkett 3d Am. Rep. at 31, 39; Singh Suppl. Rep. at 14-15); McDonald, *Migration of Talc From the Perineum to Multiple Pelvic Organ Sites: Five Case Studies With Correlative Light and Scanning Electron Microscopy*, 152(5) Am. J. Clin. Pathol. 590 (2019) ("McDonald 2019b") (Ex. 45 to Davidson Decl.) (cited in Cote Am. Rep. at 13; Clarke-Pearson 3d Am. Rep. at 12; Rep. of Bernard L. Harlow at 15, 19, Nov. 15, 2023 (Ex. 46 to Davidson Decl.); Plunkett 3d Am. Rep. at 31, 39; Singh Suppl. Rep. at 15); Johnson, *Analytic Composition of Talc in Commercially Available Baby Powder and in Pelvic Tissues Resected From Ovarian Carcinoma Patients*, 159(2) Gynecol. Oncol. 527 (2020) (Ex. 47 to Davidson Decl.) (cited in Cote Am. Rep. at 13-14; Plunkett 3d Am. Rep. at 31, 39-40; Suppl. Singh Rep. at 15, 22).

necessary to draw any causal inference. Heller 1996 observed talc in the tissue of both those who applied it perennially and those who did not. In fact, the study found "[t]alc particle counts were ***completely unrelated*** to reported levels of perineal talc exposure."[43] Thus, there is no basis to believe that either observation had anything to do with perineal dusting.

Those experts who have updated their reports since 2018 also rely on two new studies by the same research group, with McDonald as the lead author and ***three plaintiffs' experts*** as co-authors (Dr. Godleski and state-court experts Dr. Cramer and Dr. Welch), as well as a third study also co-authored by Drs. McDonald and Godleski with Johnson as the lead author.[44] The experts' primary focus is on the second McDonald study, which acknowledges that the results in Heller 1996 likely resulted from laboratory contamination and that "[p]ublished histopathologic data showing talc in pelvic organs are very limited."[45] The second McDonald study found talc particles (but no asbestos) in the pelvic tissues of five women who reported talc exposure. In only two cases did they purport to identify talc in fallopian tube tissue, which is where most serous ovarian cancer arises. The authors also reported talc particles in tissue from two of six unexposed controls and

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43 Heller 1996 at 1507 (emphasis added).

44 McDonald 2019b. Additional authors, including the lead author of both papers, Dr. McDonald, are employed by Dr. Godleski's lab.

45 McDonald 2019b at 590.

other "birefringent particles" in all six.

The authors assert that these results "support[] the contention that talc is rarely found in the pelvic tissues of nonexposed patients," but they offer no statistical analysis of the variance between the experimental and control groups (which is particularly problematic given the possibility for random error with such small sample sizes). As such, the article is, as its title indicates, a collection of "case studies," which essentially amount to anecdotal evidence. *See, e.g.*, *Slatowski v. Sig Sauer, Inc.*, No. 21-729, 2024 WL 1078198, at *6 (E.D. Pa. Mar. 12, 2024) ("Courts have frequently rejected the use of case reports to prove causation in product liability cases . . . ."), *appeal filed*; *Soldo*, 244 F. Supp. 2d at 462-64, 538. Moreover, there is no indication that the investigators charged with identifying talc particles were blinded to whether a tissue sample came from an exposed or unexposed woman. Given the substantial financial incentive those investigators had in reporting that talc can migrate, the potential for conscious or subconscious bias renders their findings entirely unreliable.

Finally, several experts cite Johnson 2020, which reported that talc particles found in ovarian tissue were of similar shape and size to those found in commercial Johnsons' Baby Powder. But the paper does not even try to explain how these compare to the size and shape of talc particles from other possible sources and therefore offers no support for the conclusion that the talc actually

comes from Johnson's Baby Powder (or anything else applied to the perineum). Again, this is, at best, anecdotal evidence that can generate hypotheses but not conclusions.

D. There Is No Reliable Evidence That Perineally-Applied Talc Can Reach The Fallopian Tubes Or Ovaries Through Inhalation Or Lymphatic Transport.

Some of plaintiffs' experts suggest that talc can be inhaled and then distributed throughout the body (including to the ovaries and fallopian tubes) by the lymphatic system,[46] though none claims that as the primary route of exposure and none explains the theory in anything but extremely perfunctory fashion.

Judge Wolfson correctly excluded this opinion, holding that it had "very little support" beyond "the ipse dixit of the expert[s]." *In re Johnson & Johnson*, 509 F. Supp. 3d at 176-77 (quoting *Soldo*, 244 F. Supp. 2d at 563). Judge Wolfson's conclusion remains correct. Most importantly, "the experts [still] fail to give any scientific support," *id.*, for their claims, and some plaintiffs' experts admitted they are aware of none.[47] To the extent the experts try to muster any

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[46] (*See* Carson Rep. at 8; Clarke-Pearson 3d Am. Rep. at 8, 12; Kane Rep. at 14; McTiernan 3d Am. Rep. at 89, 101; Rep. of Patricia G. Moorman ("Moorman Rep.") at 33, Nov. 16, 2018 (Ex. 48 to Davidson Decl.); Plunkett 3d Am. Rep. at 30; Singh Suppl. Rep. at 2; Wolf 3d Am. Rep. at 14.)

[47] (*See* Dep. of Patricia G. Moorman 303:17-304:15, Jan. 25, 2019 (Ex. 49 to Davidson Decl.) ("I can't say that there is sufficient evidence."); *see also* 1/16/19 Singh Dep. 216:5-217:6 ("I don't know which studies have evaluated . . . inhaled talc and ovarian cancer.").)

support, it falls far short. For instance, several plaintiffs' experts continue to rely on a study that reported talc in the lymph nodes of a single woman.[48] As Judge Wolfson correctly explained, that study "makes no findings as to how the talc ended up" there and cannot support an inference of inhalation. *In re Johnson & Johnson*, 509 F. Supp. 3d at 176. The other studies the experts mention are irrelevant, including one that purports to find asbestos in the lungs, pleural, and peritoneal tissue of men, not talc in the lymph or reproductive tissue of women.[49]

Additionally, the inhalation theory is contrary to common sense. *See, e.g.*, *In re TMI Litig.*, 193 F.3d 613, 683 (3d Cir. 1993) (affirming exclusion of expert opinions "because they fly in the face of reality"). If talc were really inhaled and then distributed throughout the body by the lymphatic system, then it should be able to cause cancer throughout the body—and particular in the lungs and lymph nodes. Yet, no plaintiffs' expert suggests that it causes cancer anywhere but the ovaries, and there is no epidemiological evidence to suggest that it does.

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[48] Cramer, *Presence of Talc in Pelvic Lymph Nodes of a Woman With Ovarian Cancer and Long-Term Genital Exposure to Cosmetic Talc*, 110(2) Obstet. Gynecol. 498 (2007) (Ex. 50 to Davidson Decl.) (cited in Kane Rep. at 4, 14, 15; McTiernan 3d Am. Rep. at 89-90; Singh Rep. at 18, 57; Wolf 3d Am. Rep. at 14, 15).

[49] *See* Suzuki & Kohyama, *Translocation of Inhaled Asbestos Fibers From the Lungs to Other Tissues*, 19(6) Am. J. Ind. Med. 701 (1991) (Ex. 51 to Davidson Decl.) (cited in Kane Rep. at 4, 14; Singh Rep. at 57-58; Plunkett 3d Am. Rep. at 30).

For all of these reasons, plaintiffs' experts' migration theories do not satisfy Rule 702, and their biological mechanism opinions cannot get past square one.

III. EVEN IF TALC REACHED THE FALLOPIAN TUBES OR OVARIES, PLAINTIFFS' EXPERTS HAVE NOT IDENTIFIED A PLAUSIBLE MECHANISM BY WHICH IT COULD CAUSE OVARIAN CANCER.

Plaintiffs' experts also posit that biological plausibility is satisfied because talc causes chronic inflammation and the related phenomenon of oxidative stress, and that these conditions lead to development of cancer.[50] Some also suggest that similar phenomena may affect macrophages, and thereby reduce their effectiveness in destroying malignant cells.[51] Once again, these are mere hypotheses that have been theorized in literature dominated by paid plaintiffs' experts. Judge Wolfson essentially conceded as much, but held that a "hypothesis [that] is based on scientific research and reasoning" need not be "proven" to be admissible. *In re Johnson & Johnson*, 509 F. Supp. 3d at 175. As discussed above and as amended Rule 702 makes clear, that sets the bar too low. *See, e.g.*, *In re Acetaminophen*,

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[50] (*See, e.g.*, Carson Rep. at 7; Clarke-Pearson 3d Am. Rep. at 2; Kane Rep. at 4; Levy 2d Am. Rep. at 19-20; McTiernan 3d Am. Rep. at 100-01; Moorman Rep. at 33, 34, 37; Plunkett 3d Am. Rep. at 50; 3d Am. Rep. of Jack Siemiatycki at 73-74, May 27, 2024 (Ex. 52 to Davidson Decl.); Singh Rep. at 58-59; Singh Suppl. Rep. at 13; Smith Rep. at 17-18; Smith-Bindman 3d Am. Rep. at 13-14; Wolf 3d Am. Rep. at 15-16.)

[51] (*See, e.g.*, Clarke-Pearson 3d Am. Rep. at 6; Levy 2d Am. Rep. at 14, 16; Plunkett 3d Am. Rep. at 46-47, 48; Singh Suppl. Rep. at 13.)

2023 WL 8711617, at *30 (excluding biological plausibility opinion because "[s]cientists ha[d] at best developed hypotheses"); *In re Accutane*, 511 F. Supp. 2d at 1296 (excluding biological plausibility opinion because it was "merely plausible, not proven").

A. There Is No Scientific Support For The Proposition That Perineal Talc Use Causes Chronic Inflammation Or Oxidative Stress.

Plaintiffs' experts' opinions are all premised on the idea that exposure to talc causes chronic inflammation and the subcellular phenomenon of oxidative stress. They offer no reliable evidence to support that proposition, however; nor is there any such evidence in the literature.

1. There Is No Histological Evidence Linking Talcum Powder With Chronic Inflammation.

First, there is no scientific evidence linking talc exposure with chronic inflammation. Indeed, the histological evidence that exists suggests the opposite. For example, Heller 1996 claimed to find talc in ovarian tissue, but specifically reported "no evidence of [a] response to [that] talc."[52] And other study authors who found talc in tissue likewise do not report that it induced any inflammation.[53] Plaintiffs' experts do not address these findings; for instance Dr. Cote did not even

[52] Heller 1996 at 1508.

[53] *See, e.g.*, Henderson 1971.

know whether any studies "report[ing] inflammation" had been done.[54] This failure to "account adequately for contrary evidence" further renders her biological plausibility opinions improper. *In re Zoloft*, 26 F. Supp. 3d at 461; *see, e.g.*, *In re Paraquat Prods. Liab. Litig.*, MDL No. 3004, 2024 WL 1659687, at *37 (S.D. Ill. Apr. 17, 2024) ("An expert must grapple with all relevant evidence and explain why her conclusion is scientifically justified after considering favorable and unfavorable data" rather than "disregard[] conflicting evidence."), *appeal filed*.

The few animal studies that plaintiffs' experts rely on are similarly insufficient to support their opinions. One rat study, cited by Drs. McTiernan, Wolf, and Moorman, did show "foreign body reaction[s] or infection[s]" in some rats exposed to either intravaginal or perineal talc.[55] But plaintiffs' experts ignore the primary result of the study, which is that talc ***did not*** cause neoplastic change. And the dose applied—100 mg for a 200-250 g animal, which corresponds to more than 400 mg/kg of body weight, or well over half a travel sized bottle per day for an adult human woman, was unrealistic.

Plaintiffs' experts also cite a report from the National Toxicology Program

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[54] (*See* 3/21/24 Cote Dep. 217:6-14; *see id.* 224:2-8 ("have not researched that particular question"); Dep. of Bernard L. Harlow 392:3-8, Apr. 9, 2024 (Ex. 53 to Davidson Decl.) ("I don't know of any studies" showing "inflammation in the ovar[ies] before ovarian cancer has been diagnosed").)

[55] Keskın 2009 at 927.

for the proposition that talc exposure "causes inflammation,"[56] and, according to some of the experts, contributes to cancer.[57] That report, in which mice and rats inhaled talc, was so flawed that the FDA later concluded it had "no relevance to human risk."[58] Even at face value, it did not report any adverse effects in the ovaries; rather, it found cancer in the lungs and adrenal glands of rats—but notably not mice. Only Dr. Plunkett confronts this fact, and she merely asserts that "based on an inhalation route of exposure . . . the studies would not be expected to produce ovarian tumors."[59]

Finally, several experts make passing reference to pleurodesis, a medical procedure in which talc is injected in huge doses to intentionally induce acute inflammation.[60] But as Dr. Plunkett concedes, the procedure produces "acute

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[56] (Wolf 3d Am. Rep. at 16; *see* Clarke-Pearson 3d Am. Rep. at 6 ("known to elicit an inflammatory response") (both citing National Toxicology Program, *Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6) in F344/N Rats and B6C3F1 Mice (Inhalation Studies)* (1993) ("NTP 1993") (Ex. 54 to Davidson Decl.).)

[57] (*See* Plunkett 3d Am. Rep. at 43-45; McTiernan 3d Am. Rep. at 93-94 (citing NTP 1993).)

[58] (Letter from Steven M. Musser, Ph.D., Deputy Dir. For Sci. Operations, Ctr. For Food Safety & Applied Nutrition, to Samuel S. Epstein, M.D., Cancer Prev. Coalition, Univ. of Ill. – Chi. School of Pub. Health, at 2, 4 (Apr. 1, 2014) (Ex. 55 to Davidson Decl.).)

[59] (*See* Plunkett 3d Am. Rep. at 45.)

[60] (*See* McTiernan 3d Am. Rep. at 90; Moorman Rep. at 33-34; Plunkett 3d Am. Rep. at 52-53.)

[inflammation], not a chronic response as is [supposedly] characteristic of carcinogenesis."[61] In any event, pleurodesis can be done with several different substances; it is the presence of a foreign body in large quantity that causes inflammation, not any special characteristic of talc. And if pleurodesis were relevant, it would undermine plaintiffs' position, since long-term studies show that patients who undergo the procedure do not have increased rates of cancer.[62]

2. There Is No Subcellular Evidence Linking Talc With Chronic Inflammation Or Oxidative Stress.

Plaintiffs' experts also rely on a series of studies that purport to show changes to subcellular markers of inflammation or oxidative stress. These studies do not support the conclusions the experts draw from them.

For starters, all of them were performed *in vitro*—i.e., in a test tube rather than a live animal, much less a human. Such studies are always "one step removed from directly proving causation," *In re Human Tissue*, 582 F. Supp. 2d at 663, and cannot be applied "directly to the human experience," *Wade-Greaux*, 874 F. Supp. at 1484. Indeed, they are even less "helpful" than animal studies. *In re Human Tissue*, 582 F. Supp. 2d at 663. Judge Wolfson acknowledged as much, but held

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61 (*See* Plunkett 3d Am. Rep. at 53.)

62 *See, e.g.*, Research Committee of the British Thoracic Association and The Medical Research Council Pneumoconiosis Unit, *A Survey of the Long-Term Effects of Talc and Kaolin Pleurodesis*, 73 Br. J. Dis. Chest 285 (1979) (Ex. 56 to Davidson Decl.).

that "such studies 'can provide a reliable basis for medical and scientific opinions as long as their extrapolations are warranted'" and based on "good grounds." *In re Johnson & Johnson*, 509 F. Supp. 3d at 136. But plaintiffs' experts do not even attempt to provide such grounds, which would require explaining how the artificial conditions of a test tube can be applied to a whole human being. For this reason alone, their use of these studies to construct a plausible biological mechanism is unreliable.

In addition, the literature plaintiffs' experts cite provides them no support even *in vitro*. The experts rely most heavily on Fletcher 2019, a study from the laboratory of former expert Dr. Saed.[63] That study largely writes up the work Dr. Saed performed for this litigation by repurposing his now-withdrawn expert report.[64] When Dr. Saed was offered directly, Judge Wolfson prohibited him from linking talc to ovarian cancer or to common gene mutations called single nucleotide polymorphisms ("SNPs"), but permitted him to opine that talc caused

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[63] Fletcher, *Molecular Basis Supporting the Association of Talcum Powder Use With Increased Risk of Ovarian Cancer*, 26(12) Reprod. Sci. 1603 (2019) ("Fletcher 2019") (Ex. 57 to Davidson Decl.) (cited in Levy 2d Am. Rep. at 16; McTiernan 3d Am. Rep. at 91; Singh Suppl. Rep. at 15; Smith-Bindman 3d Am. Rep. at 14-15; Wolf 3d Am. Rep. at 16).) As with the Harper paper, discussed elsewhere, Dr. Saed was the corresponding author despite Dr. Fletcher's name listed first.

[64] Although this work was funded by plaintiffs' counsel, the article incorrectly states that "[t]he author(s) received no financial support" for it. Fletcher 2019 at 9.

oxidative stress. *In re Johnson & Johnson*, 509 F. Supp. 3d at 136-40, 175. The current experts use the Saed and Fletcher research for exactly what Judge Wolfson held it cannot show: that talc causes cancer.[65]

This is doubly problematic because the Fletcher paper does not even reliably support a narrower opinion on oxidative stress. As a threshold matter, there are substantial reasons to think that the data reported cannot be trusted, since a review of his laboratory notebooks suggests extraordinarily sloppy work, if not outright fabrication of the results. To take just a few examples, portions of the lab notebook are whited out with contradictory information written over, and basic mathematical calculations (like averages) are done incorrectly. The treatment time is reported as 48 hours, which is consistent with Dr. Saed's initial and rejected manuscript, but inconsistent with the published article, which claimed 72 hours of treatment. Nevertheless, Judge Wolfson found that despite "careless mistakes and shoddy record keeping," Dr. Saed's team had not "altered" the data "in bad faith."

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[65] (*See* Smith-Bindman 3d Am. Rep. at 15 ("These findings . . . provide a molecular mechanism to previous reports linking genital talc use to increased ovarian cancer risk") (quoting Fletcher 2019); McTiernan 3d Am. Rep. at 91 ("providing a molecular basis for epidemiologic studies demonstrating an increased risk of ovarian cancer"); Singh Suppl. Rep. at 14-15 (treating Fletcher among studies "which have provided further evidence in support of a causal association"); *see also* Levy 2d Am. Rep. at 16 (citing Fletcher's CA-125 findings, which Judge Wolfson found are "not a reliable measure of the risk of ovarian cancer resulting from talc use," *In re Johnson & Johnson*, 509 F. Supp. 3d at 139); Wolf 3d Am. Rep. at 17 (similar).)

In re Johnson & Johnson, 509 F. Supp. 3d at 146.

Even if the data reported in the Fletcher paper were genuine, they would not show talc causes oxidative stress. For one thing, the authors made no attempt to use a physiologically relevant dose. *See, e.g.*, *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 478 (E.D. Pa. 2014) (excluding opinions based on *in vitro* studies "well above the maximum recommended human dose"); *In re Diet Drugs (Phentermine, Fenfluramine, Dexfenfluramine) Prods. Liab. Litig.*, MDL No. 1203, 2000 WL 962545, at *11 (E.D. Pa. June 28, 2000) (excluding *in vitro* study that used dose markedly larger than "clinically relevant concentration[s]"). Judge Wolfson dismissed this problem, positing that without a direct causal claim, "the question of dose is less critical." *In re Johnson & Johnson*, 509 F. Supp. 3d at 143. But if the dose used in the study is not analogous to the dose experienced in real life, there is no reason to believe that the observations in the study would be replicated in real life. That is true whether those observations relate to oxidative stress or to carcinogenesis. Even more fundamentally, the Fletcher paper did not actually find oxidative stress. Instead, it found changes in the expression of certain pro- and anti-oxidant enzymes—an "indirect[]"[66] measure, which may or may not translate to a net

[66] (Dep. of Ghassan Saed 304:7-10, 306:21-307:24, Jan. 23, 2019 (Ex. 58 to Davidson Decl.).)

change in cellular redox balance.

Other papers on which the experts rely provide even less support. For instance, several experts cite an *in vitro* study on gene expression by Shukla et al.,[67] seizing on changes in the expression of genes "relate[d] to oxidative stress and inflammation"[68] in human ***mesothelial*** cells. But the Shukla study undermines plaintiffs' theories because it showed "no significant . . . changes" in ***ovarian*** cells, and even in irrelevant mesothelial cells, it showed that any changes were gone by 24 hours, "suggesting that [those] cells adapt to or undergo repair."[69] For this reason, too, the literature on which the experts rely does "not adequately support" their inflammation opinions. *In re Zoloft*, 26 F. Supp. 3d at 462.[70]

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[67] Shukla, *Alterations in Gene Expression in Human Mesothelial Cells Correlate with Mineral Pathogenicity*, 41(1) Am. J. Respir. Cell Mol. Biol. 114 (2009) ("Shukla 2009") (Ex. 59 to Davidson Decl.).

[68] (Plunkett 3d Am. Rep. at 46; *see also, e.g.*, McTiernan 3d Am. Rep. at 92; Clarke-Pearson 3d Am. Rep. at 6.)

[69] Shukla 2009 at 120. Similar results were seen in another study by the same research group that only Dr. Plunkett even bothers to mention: Hillegass, *Utilization of Gene Profiling and Proteomics to Determine Mineral Pathogenicity in a Human Mesothelial Cell Line (LP9/TERT-1)*, 73(5-6) J. Toxicol. Environ. Health 423 (2010) (Ex. 60 to Davidson Decl.). Dr. Plunkett claims the dose of talc was too low, but does not explain what it should have been or how it compares to the amount of talc to which a cell would be exposed in vivo.

[70] Some plaintiffs' experts also point to a study that purported to show "increased reactive oxygen species" in mouse macrophages. (Clarke-Pearson 3d Am. Rep. at 6 (citing Mandarino 2020); *see also* Cote Am. Rep. at 14; Levy 2d Am. Rep. at 16 (similar).) But macrophages have no relevance to neoplastic transformation in ovarian cells.

3. Plaintiffs' Experts Cannot Reliably Link Chronic Inflammation To Ovarian Cancer.

Plaintiffs' experts also lack reliable evidence to show that chronic inflammation can cause any kind of ovarian cancer. To the contrary, one study that looked for signs of inflammation in ovarian tissue samples determined that "no significant correlation was made between serous carcinoma and histological signs of inflammation."[71] Although the authors observed certain nonsignificant trends, they noted that the cancer group was older and age represented a confounder. None of plaintiffs' experts mentions this study, further indicating their unwillingness to confront evidence that does not support them. *See In re Zoloft*, 26 F. Supp. 3d at 461. But even if inflammation were correlated with cancer, it would not show causation since cancer itself may cause inflammation.[72]

Plaintiffs' experts offer several lines of argument to link chronic inflammation to ovarian cancer, but all of them lack support. The experts rely heavily on a series of review articles, which do not contain any original data but purport to synthesize existing literature. Such articles are only as valuable as the

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[71] Malmberg, *Serous Tubal Epithelial Carcinoma, Chronic Fallopian Tube Injury, and Serous Carcinoma Development*, 468(6) Virchows Arch. 707, 712 (2016) (Ex. 61 to Davidson Decl.).

[72] A study by defense expert Dr. Ie-Ming Shih, which plaintiffs' experts have not challenged, demonstrates as much. (*See* Rep. of Ie-Ming Shih, Feb. 25, 2019 (Ex. 62 to Davidson Decl.); *see also* 3/21/24 Cote Dep. 222:24-223:4 (cancer can cause inflammation).)

studies that underlie them, and if an expert does not analyze the underlying studies, he cannot reliably rely on a review article. *See Mallozzi v. EcoSMART Techs., Inc.*, No. 11-2884, 2013 WL 2415677, at *7 (E.D.N.Y. May 31, 2013) (excluding expert who failed to "justif[y] his reliance" on a review article and "provided no analysis of . . . the clinical trials that were reviewed in the article"); *Soldo*, 244 F. Supp. 2d at 542 (statements in a treatise are "no more reliable" than the underlying data on which they rely). The review articles do not, in any event, support the experts' claims. For example, Ness and Cottreau,[73] a 25-year-old article, proposed inflammation as a "novel hypothesis," not an established mechanism. A few experts cite a similarly outdated review article, Balkwill and Mantovani,[74] but that paper is not focused on ovarian cancer.

The original research on which plaintiffs' experts rely is no more helpful. Many cite a paper by Buz'Zard and Lau[75] for the proposition that talc causes

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[73] Ness & Cottreau, *Possible Role of Ovarian Epithelial Inflammation in Ovarian Cancer*, 91(17) J. Nat'l Cancer Inst. 1459, 1459 (1999) (Ex. 63 to Davidson Decl.) (cited in Kane Rep. at 10; Singh Rep. at 18, 58; Wolf 3d Am. Rep. at 15).

[74] Balkwill & Mantovani, *Inflammation and Cancer: Back to Virchow?*, 357(9255) Lancet 539 (2001) (Ex. 64 to Davidson Decl.) (cited in Clarke-Pearson 3d Am. Rep. at 5; Moorman Rep. at 34; Smith-Bindman 3d Am. Rep. at 10; Wolf 3d Am. Rep. at 15).

[75] Buz'Zard & Lau, *Pycnogenol® Reduces Talc-Induced Neoplastic Transformation in Human Ovarian Cell Cultures*, 21(6) Physiotherapy Research 579 (2007) (Ex. 65 to Davidson Decl.) (cited in Carson Rep. at 6; Clarke-Pearson

(cont'd)

changes to levels of reactive oxygen species ("ROS"), cell proliferation, and, some suggest, neoplastic change. Read fairly, that paper not only fails to support their theories, but undercuts them. Buz'Zard and Lau showed that almost every talc treatment in immortalized ovarian cells ***decreased*** ROS levels, which were seen as a measurement of oxidative stress. Cell proliferation also ***decreased*** at the highest dose of talc treatment, even though increased cell proliferation suggests cancer risk. So did soft agar growth, which the authors (incorrectly) treated as a proxy for cell transformation.[76]

Some of plaintiffs' experts also cite a paper by Trabert and colleagues[77] that reports a slight association between certain inflammatory biomarkers and ovarian cancer. The study measured 46 inflammatory markers; only three showed associations; and with respect to one, the authors warned that the sample size was so small the results should be interpreted with caution. When applying stricter standards to account for false positives (a common approach when testing many

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3d Am. Rep. at 6, 14; Cote Am. Rep. at 14; Kane Rep. at 10, 11, 36; McTiernan 3d Am. Rep. at 91; Plunkett 3d Am. Rep. at 45; Singh Rep. at 19, 59).

[76] High doses of talc increased rates of soft agar growth in ovarian ***stromal*** cells, but those are not relevant to epithelial ovarian cancer.

[77] Trabert, *Pre-Diagnostic Serum Levels of Inflammation Markers and Risk of Ovarian Cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial*, 135(2) Gynecol. Oncol. 297 (2014) (Ex. 66 to Davidson Decl.) (cited in Clarke-Pearson 3d Am. Rep. at 5; Kane Rep. at 12; Plunkett 3d Am. Rep. at 50).

variables at once), only ***one*** (CRP) remained significant. In any event, even assuming the correlations were not spurious, it is probable that cancer or precancerous lesions cause inflammatory markers, rather than the other way around. When the results were limited to samples collected more than five years before diagnosis in order to account for this possibility, only two associations were reported using conventional statistics—almost exactly what would be expected by chance—and the authors did not report any results adjusted for multiple comparisons.

Several plaintiffs' experts also claim that endometriosis is associated with ovarian cancer,[78] but, as mentioned above, endometriosis is ***not*** associated with high grade serous cancer, by far the most common subtype,[79] and the one which some plaintiff's experts suggest is most clearly related to talc use. Some experts note a recent paper by Phung and colleagues, which compared associations between talc and cancer in women with and without endometriosis, claiming that it showed "a greater increased risk of ovarian cancer with genital talc use in women with endometriosis . . . versus those without."[80] But the study did not show any

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78 (*See* Kane Rep. at 35; Levy 2d Am. Rep. at 14; Smith-Bindman 3d Am. Rep. at 9-10.)

79 *See supra* at 11 & n.9 (citing Reid 2017).

80 (Wolf 3d Am. Rep. at 4; *see, e.g.*, Cote Am. Rep. at 17; Singh Suppl. Rep. at 21 (all citing Phung, *Effects of Risk Factors for Ovarian Cancer in Women With*

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significant interaction between talc and endometriosis. Although the point estimate for the association between talc and cancer was very slightly higher for women with endometriosis than those without, the p-for-interaction was 0.65, meaning the difference was so small it was ***more likely than not*** to occur due to chance.

As for anti-inflammatory medication, plaintiffs cherry-pick supportive results, while ignoring contrary ones, often from the very same studies. For instance, Dr. Wolf cites a 2019 pooled analysis by Trabert and colleagues[81] that found a barely-significant association between cancer and frequent aspirin use for less than five years (although it did not account for the possibility of false positives due to the many variables tested). But it also showed no significant association for either long-term aspirin use or for other anti-inflammatory drugs regardless of duration, and in some cases suggested a non-significant protective effect. Even Dr. Smith explained that the study taken as a whole showed "no effect of aspirin or [non-steroidal anti-inflammatory drugs] on ovarian cancer risk."[82]

Other experts cite an earlier pooled analysis by the same lead author that

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and Without Endometriosis, 118(5) Fertil. Steril. 960 (2022) (Ex. 67 to Davidson Decl.)).)

81 Trabert, *Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium*, 111(2) J. Nat'l Cancer Inst. 137 (2019) (Ex. 68 to Davidson Decl.) (cited in Wolf 3d Am. Rep. at 16).

82 (Smith Rep. at 18.)

reported similarly inconsistent results, suggesting a protective effect for aspirin but not other anti-inflammatory medications.[83] And Dr. Levy also cites a recent study by Hurwitz and colleagues that shows a small protective effect for aspirin use, without testing any other medication.[84] But none of the experts squares these studies with others showing no significant association between aspirin and cancer.[85] Perhaps more importantly, they do not even bother to explain why only one anti-inflammatory medication would reduce risk if inflammation were really a driver of cancer.

Finally, in an effort to demonstrate a direct link between talc and cancer, plaintiffs' experts rely heavily on Dr. Saed's recent paper published with Amy Harper as the nominal lead author,[86] which they contend directly demonstrates

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83 *See* Trabert, *Aspirin, Nonaspirin Nonsteroidal Anti-Inflammatory Drug, and Acetaminophen Use and Risk of Invasive Epithelial Ovarian Cancer: A Pooled Analysis in the Ovarian Cancer Association Consortium*, 106(2) J. Nat'l Cancer Inst. 1 (2014) (Ex. 69 to Davidson Decl.) (cited in Kane Rep. at 12; Levy 2d Am. Rep. at 14; McTiernan 3d Am. Rep. at 90).

84 Hurwitz, *Association of Frequent Aspirin Use with Ovarian Cancer Risk According to Genetic Susceptibility*, 6(2) JAMA Network Open e230666 (2023) (Ex. 70 to Davidson Decl.) (cited in Levy 2d Am. Rep. at 14).

85 *See, e.g.*, Baandrup, *Nonsteroidal Anti-Inflammatory Drugs and Risk of Ovarian Cancer: Systematic Review and Meta-Analysis of Observational Studies*, 92(3) Acta. Obstet. Gynecol. Scand. 245 (2013) (Ex. 71 to Davidson Decl.); Ni, *Meta-Analysis on the Associations Between Non-Steroidal Anti-Inflammatory Drug Use and Ovarian Cancer*, 75(1) Br. J. Clin. Pharmacol. 26 (2012) (Ex. 72 to Davidson Decl.).

86 Harper 2023.

malignant transformation.[87] It does no such thing, as made clear by the peer reviewers at reputable journals, who resoundingly rejected it. A reviewer for Reproductive Sciences stated flatly that the findings "would not establish that it is biologically plausible that talc causes ovarian cancer,"[88] while a reviewer from Gynecologic Oncology said they offered "no . . . mechanistic insight."[89] One of the reviewers for PLOS ONE was even blunter, calling any claimed link between talc and carcinogenesis based on the study "outrageous and not supported by the manuscript's data."[90]

This alone is reason to exclude any expert who relies on the paper. When she limited Dr. Saed as a witness, Judge Wolfson did so in part "bolstered by[] comments [he] received from peer reviewers at" Gynecologic Oncology. *In re Johnson & Johnson*, 509 F. Supp. 3d at 137. That reasoning applies with even greater force here, given that his follow-up article was rejected wholesale by at least three journals, including Reproductive Science, which published Dr. Saed's

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87 Preposterously, the authors claimed that malignant transformation took just 72 hours. No expert has ever been able to defend that claim. Dr. Clarke-Pearson, for instance, acknowledged that for inflammation to lead to malignant transformation takes "decades." (Dep. of Daniel L. Clarke-Pearson 83:3-84:1, Jan. 17, 2024 (Ex. 73 to Davidson Decl.).)

88 (SAED_SEPT222021_SUPPL_000128.)

89 (SAED_SEPT222021_SUPPL_000070.)

90 (SAED_SEPT222021_SUPPL_000101.)

first paper. The purpose of peer review is to "increase[] the likelihood that substantive flaws in methodology will be detected," *Daubert*, 509 U.S. at 593—and in this case, peer reviewers found "substantive flaws" in spades.

As one reviewer put it, the substantive flaws in the Harper paper are "too numerous to count, and the science, methodology, and data cannot be trusted."[91] A review of even a few of the substantive flaws that the reviewers identified makes clear that the article and any expert opinions that rely on it constitute junk science:

- ***Dose.*** The dose of talc applied, by the authors' own admission, did not "represent a typical dose" to which a woman would be exposed.[92] The reviewers noted that the dose was "extremely high"[93] and the authors of the paper did not make any effort to justify these atypical doses.[94]
- ***Cell lines.*** The cells used did not come from the fallopian tubes, where epithelial ovarian cancer arises.[95] Such cells are commercially available, but the authors made no explanation of why they did not

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91 (SAED_SEPT222021_SUPPL_000104.)

92 Harper 2023 at 155. In actuality, the dose was not even reported. The authors reported the concentration of the solution they used but not the quantity.

93 (SAED_SEPT222021_SUPPL_000070.)

94 (SAED_SEPT222021_SUPPL_00128; *see, e.g.*, SAED_SEPT222021_SUPPL_000103 ("Where is the explanation that these doses are even relevant?").)

95 (SAED_SEPT222021_SUPPL_000069.)

use them.[96]

- ***Mathematical Errors.*** The authors performed statistical tests that were wholly inappropriate for the data collected,[97] and reported mathematically impossible results (such as nonsensical 11% and 20% increases over zero).
- ***Cell seeding.*** The cells were seeded with a "very high density"—perhaps 90 times above normal.[98] That is important because the cell reactions that the authors observed may represent a "stress response" to high density.[99]

Most importantly, despite claims by both the authors and plaintiffs' experts, the study ***does not actually show malignant (i.e., cancerous) transformation***; nor does it show neoplastic transformation (i.e., the development of tumor-like properties). Instead, it shows growth in soft agar. As the reviewers noted, that is not the same thing, and "not enough data to claim malignant transformation.[100]

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96 (*Id.*)

97 (*See* SAED_SEPT222021_SUPPL_000102; SAED_SEPT222021_SUPPL_000070.)

98 (SAED_SEPT222021_SUPPL_0001012.)

99 (*See id.*)

100 (*See* SAED_SEPT222021_SUPPL_000101; SAED_SEPT222021_SUPPL_000103; *see also* SAED_SEPT222021_SUPPL_000128 (recommending injection into animal model).)

One reviewer explained that the assay used "has not been established,"[101] while another was blunter, stating that he "did not see any carcinogenic assays" or "any methodology for detecting malignant transformations."[102] To produce results relevant to cancer, the authors would need a "more diverse battery of tests," to consider "the key characteristics that define a carcinogen,"[103] and to replicate the results in live animals.[104] For these reasons, reviewers concluded that the study "cannot be trusted"[105] and is "of limited relevance."[106]

In short, plaintiffs' experts' opinions fail at every step of the hypothesized causal chain, requiring that they be excluded from trial.

B. Plaintiffs' Experts' Macrophage-Inhibition Theory Is Not Biologically Plausible Either.

Relying entirely on two recent *in vitro* studies by an overlapping group of authors, some plaintiffs' experts propose an alternative theory that is even more devoid of support: that talc has a "negative impact on" the function of

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101 (SAED_SEPT222021_SUPPL_000069.)

102 (SAED_SEPT222021_SUPPL_000103.)

103 (SAED_SEPT222021_SUPPL_000101.)

104 (SAED_SEPT222021_SUPPL_000128.) Notably, when he was an expert witness, Dr. Saed himself acknowledged this fact. (*See* Dep. of Ghassan Saed 542:20-21, Feb. 14, 2019 (Ex. 74 to Davidson Decl.).)

105 (SAED_SEPT222021_SUPPL_0001014.)

106 (SAED_SEPT222021_SUPPL_000069.)

macrophages, immune cells that can destroy cancer cells.[107] The first study, with Mandarino as its lead author and several plaintiffs' experts as co-authors, purported to show that talc-treated macrophages were less effective at destroying surface ovarian cells used as a model for ovarian cancer than untreated macrophages, and also reported changes to ROS production and certain gene expression. The second, with Emi as its lead author, reported gene expression changes in talc-treated macrophages in greater detail. This theory is even more speculative than plaintiffs' inflammation theory.

As a threshold matter, absent any showing that talc can lead to malignant transformation, any impairment of the macrophage response to malignant cells is irrelevant. In any event, the results do not show impaired macrophage response. The macrophage cells came from mice, not humans, meaning the studies combined the limitations inherent in *in vitro* studies with the limitations inherent in animal studies.[108] *See, e.g.*, *In re Human Tissue*, 582 F. Supp. 2d at 657 (limits to extrapolating from animal studies). Moreover, the mouse cells were treated with a

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[107] (Smith-Bindman 3d Am. Rep. at 10, 14 (citing Mandarino 2020 & Emi, *Transcriptomic and Epigenomic Effects of Insoluble Particles on J774 Macrophages*, 16(10) Epigenetics 1053 (2021) ("Emi 2021") (Ex. 75 to Davidson Decl.)); *see* Levy 2d Am. Rep. at 16; Singh Suppl. Rep. at 13, 15, 22 (similar).)

[108] Plaintiffs' experts acknowledge the results have not been replicated in human cells. (*See* Dep. of Laura M. Plunkett ("8/10/21 Plunkett Dep.") 259:1-12, Aug. 10, 2021 (Ex. 76 to Davidson Decl.); Dep. of Rebecca Smith-Bindman 124:10-21, Mar. 20, 2024 (Ex. 77 to Davidson Decl.).)

non-physiological concentration of estrogen of 2 µg/mL. The authors admitted that this concentration was "at the higher end," but defended it on the ground that estrogen concentration "is more than 100-fold higher" in the ovaries than in blood serum.[109] Even if that were true, the treatment remains excessive by at least an order of magnitude. Estrogen serum levels are "in the range of pg/mL to ng/mL,"[110] while the 2 µg corresponds to 2,000,000 pg or 2,000 ng—i.e., thousands to millions of times higher. Plaintiffs' experts entirely ignore this fact.[111] And even in these highly artificial conditions, the authors made no claims that any of the observed changes were clinically significant. For instance, the Mandarino paper noted a 10-20% increase in the number of surviving tumor cells, which may or may not have any *in vivo* significance.

It is likely for all these reasons that both studies stopped well short of mechanistic conclusions, instead stating only that the findings should "prompt further studies"[112] and raise a "hypothesis that merits further testing."[113] That the experts in this case "'exceed the limitations the authors themselves placed on the

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109 Mandarino 2020 at 9.

110 *Id.*

111 (*See, e.g.*, 8/10/21 Plunkett Dep. 260:15-261:4 (responding to a question about dose with "I haven't done that analysis").)

112 Mandarino 2020 at 1.

113 Emi 2021 at 1068.

stud[ies]'" further demonstrates the unreliability of their opinions. *Daniels-Feasel v. Forest Pharms., Inc.*, No. 17-4188, 2021 WL 4037820, at *4, *9 (S.D.N.Y. Sept. 3, 2021) (citation omitted) (excluding Dr. Plunkett, among others), *aff'd*, No. 22-146, 2023 WL 4837521 (2d Cir. Jul 28, 2023). Accordingly, the macrophage theory, too, should be excluded.

CONCLUSION

For the foregoing reasons, all of plaintiffs' experts' opinions on proposed biological mechanisms are unreliable, and they should all be excluded.

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Respectfully submitted,

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